REMARKS

This responds to the Office Action mailed March 1, 2007. Claims 1-13 are pending in the application. Claims 8-10 and 13 are withdrawn from consideration. Claims 2 and 3 are canceled. Claims 1, 4 and 11 have been amended. No new matter is added with the amendment. With the entry of this Amendment, claims 1-7, 11 and 12 are pending for consideration.

I. Information Disclosure Statement

According to the Examiner, the information disclosure statement filed February 14, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it contains foreign references without English translations. The documents WO 2000/46585 and Alexander Goetz, Bioforum 2001 have not been considered and are crossed through on the IDS which is included in the mailing of this action. Applicant is requested to submit an English translation of the documents for them to be considered in prosecution of this application. In response Applicants enclose a copy of USP 7,211,433, which is based on WO 2000/46585. Furthermore, with regard to the Goetz article, applicants are not required to provide a translation so long as the relevance of this document is described in the IDS. Applicants herewith provide such a description of the relevance by translating the abstract of this article. This comports with all regulatory requirements; indication of consideration is therefore respectfully requested.

II. Specification

The disclosure is objected to because of the following informalities: the specification contains typographical errors. For example, on page 29 line 17 "bond marrow" should be "bone marrow". The Examiner notes that appropriate correction is required throughout. In response, applicants submit the above amendment to the specification.

The use of the trademarks Ficoll®, Oncoquick®, Leucosep®, and LightCycler® have been noted in this application. They should be capitalized wherever they appear

and be accompanied by the generic terminology. In response, applicants herewith submit the above amendment. However, applicants point out that the above trade names are given generic descriptions only once in the application. Ficoll® is described at page 6, first paragraph. Oncoquick® is described in the specification at page 17 in the second paragraph of Example 1. Leucosep® is described at page 17, in the third paragraph of Example 1. LightCycler® is described at page 18. No new matter is added with any of the amendments.

The Examiner further asserts that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. The Examiner notes that trademark symbols are missing for LightCycler® on page 18, Oncoquick® on page 30, and Ficoll® on page 29. In response, appropriate correction has been made for all trademarks throughout with the above amendment.

III. Claim Rejections - 35 USC § 112

Claims 1-7, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, for the asserted reason that the specification does not reasonably provide enablement for detecting disseminated tumor cells, wherein the enriched cells express cytokeratins 1-7, and 9-17. The Examiner bases this conclusion on a perceived lack of predictability in the art and lack of established protocols. The Examiner states, however, that the claims are enabled for a method for detecting disseminated tumor cells from body fluids by density gradient separation in a vessel divided by a porous barrier, a filter, a sieve or a flap, wherein the enriched cells express cytokeratins 8, 18, 19, and 20.

Applicants respectfully traverse this rejection as it may be applicable to the amended claims. The method of amended claim 1 combines former claims 1 to 3. This method comprises the separation of non-tumor from tumor cells, which both express at least one of cytokeratins 1-20. A subsequent RT-PCR reaction allows one to detect the

tumor cells by their endothelial marker cytokeratin. The method is exemplified in Example 2 with the detection of CK-20.

No US law or regulation requires applicants to exemplify each and every embodiment encompassed by the claims. And, contrary to the Examiner's conclusion, the specification provides enough instructions to permit one of skill in the art to practice the full scope of the invention, including the performance of RT-PCR reactions for cytokeratins 1-19. The selection of suitable PCR primers for the amplification reaction for detecting cytokeratin markers 1-19 represents a standard procedure for a skilled artisan. That is, in order to obtain suitable primers, only the nucleotide sequence of the desired marker is needed. The nucleotide sequences for cytokeratins 1-20 can easily be obtained from the NCBI-database. In this regard, the present specification discloses that CK-20 is deposited in the NCBI-database under accession No. BC031559 (specification at page 12, lines 29-33). The specification clearly describes other primers that can be derived from the known cytokeratin sequences. Other examples for cytokeratin sequences that can easily be obtained from this database, are KRT1 (cytokeratin 1): NM_006121; KRT2 (cytokeratin 2): NM_000423 and KRT3 (cytokeratin 3): NM_057088. Applicants assert that even obtaining specific primers from cytokeratin sequences represents a standard procedure for a skilled artisan. In view of the well-developed and well-accepted protocols applicable to this invention, applicants need not show the applications of such tools for each species encompassed by the claims. Although some experimentation is needed, such experimentation is customary for the field of the claimed invention. Such experimentation is not unreasonable and no undue.

The Examiner's arguments with regard to the predictability of the present invention and reliance upon the teachings of Traweek *et al.* and Slade and Coombs, is misplaced. This is so because claim 1 is directed to the detection of cytokeratin 1-20 markers of cytokeratin 1-20 expressing tumor cells. The present invention is not directed to the detection of any tumor cells using cytokeratin 1-20 –markers. Thus, it is not relevant that the cited references teach that cytokeratins 8, 18 and 19 are not independently reliable for the detection of disseminated cancer cells generally.

Applicants do not intend to detect all tumor cells, rather applicant's invention is directed to the use of cytokeratin 1-20 specific primers using RT- PCR to detect cytokeratin 1-20 expressing tumor cells. Such detection is predictable. In view of this explanation, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

IV. Conclusion

Applicants acknowledge that claims 1-7, 11, and 12 are free of the prior art and that the Examiner believes that the closest prior art is Dahm *et al.* (U.S. Pat 6,821,726, PCT filed August 12, 1999).

CONCLUSION

In light of the above amendments and comments, Applicant respectfully requests that all rejections and objections be withdrawn and that a timely Notice of Allowance should be issued in this application. Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: June 1, 2007

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